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Signed R. Mahoney

Dated 19 October 2004

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your Reference — AP/PB60564P

13NOV03 E851683-1 002039
P01/7700 0.00-0326407.4

2. Patent application number *(The Patent office will fill in this part)* — 0326407.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its corporation — GB

4 Title of the invention — CHEMICAL COMPOUNDS

5 Name of your agent *(if you know one)* — PETER DOLTON

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. Divisionals: etc Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier application	Date of filing (day / month / year)

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body

Otherwise answer NO See note (d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	-
Description	39
Claim(s)	4
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patent Form 9/77)*

Request for substantive examination *(Patent Form 10/77)*

Any other documents *(please specify)*

11. **I/We request the grant of a patent on the basis of this application**

Signature **PETER DOLTON.** **Date 12 November 2003**
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

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Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

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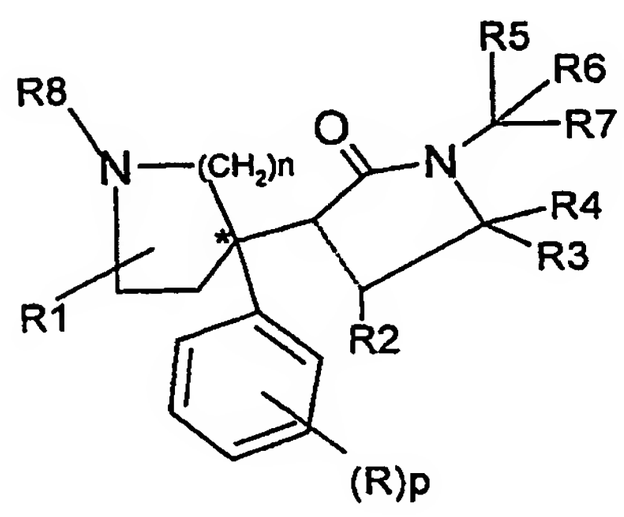
PB60564P

Chemical Compounds

The present invention relates to lactam derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The present invention thus provides compounds of formula (I)



(I)

Wherein

---- represents single or double bond;

R represents halogen, C_{1-4} alkyl, cyano, C_{1-4} alkoxy, trifluoromethyl or trifluoromethoxy;

R_1 represents hydrogen, halogen, C_{3-7} cycloalkyl, hydroxy, nitro, cyano or C_{1-4} alkyl optionally substituted by one or two groups selected from halogen, cyano, hydroxy or C_{1-4} alkoxy;

R_2 represents hydrogen or C_{1-4} alkyl;

R_3 represents hydrogen, hydroxy or C_{1-4} alkyl;

R_4 represents hydrogen or R_4 together with R_3 represents =O;

R_5 represents phenyl, naphthyl, a 9 to 10 membered fused bicyclic heterocyclic group or a 5 or 6 membered heteroaryl group, wherein said groups are optionally substituted by 1 to 3 groups independently selected from trifluoromethyl, C_{1-4} alkyl, hydroxy, cyano, C_{1-4} alkoxy, trifluoromethoxy, halogen or $S(O)qC_{1-4}$ alkyl;

R_6 and R_7 independently represent hydrogen, cyano, C_{1-4} alkyl or R_3 together with R_4 represents C_{3-7} cycloalkyl;

R_8 represents $(CH_2)rR_9$;

R_9 represents hydrogen or C_{3-7} cycloalkyl;

n represents 1 or 2;

p is zero or an integer from 1 to 3;

q is 0, 1 or 2;

r is 0 or an integer from 1 to 4;

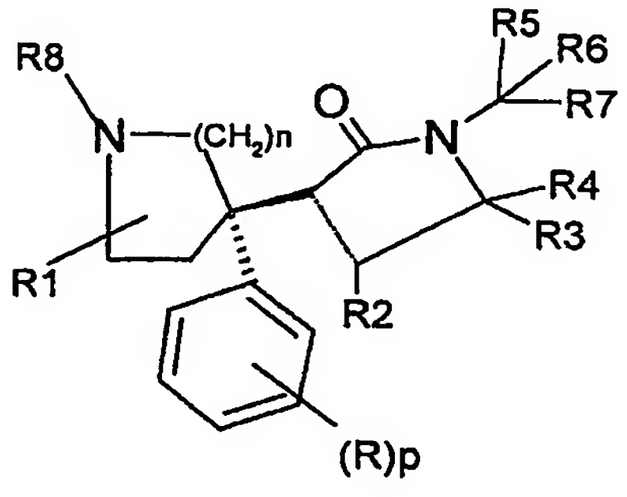
and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, trifluoroacetates, acetates, citrates, succinates, tartrates, lactates, malates, fumarates and maleates.

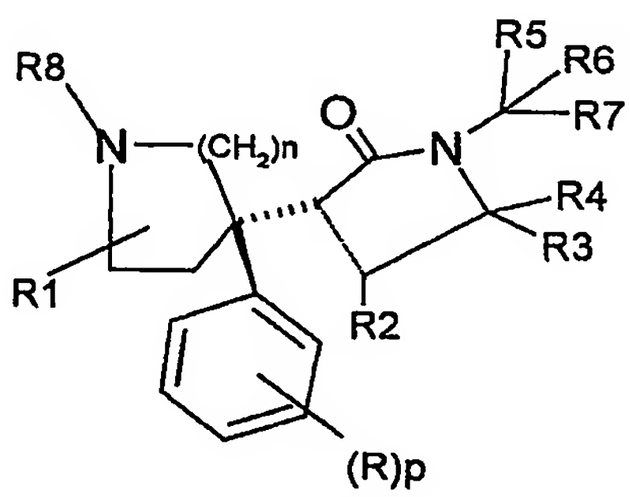
The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts and their pharmaceutically acceptable solvates.

It will be appreciated by those skilled in the art that the compounds of formula (I), when n is 1 and when n is 2 and R_1 is not hydrogen, contain at least one chiral centre (namely the carbon atom shown as * in formula (I)) and may be represented by formula (1a) and (1b).



(1a)



(1b)

The wedged bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

Further asymmetric carbon atoms are possible when R_3 and R_4 are not the same group and/or R1 is different from hydrogen and/or R_2 is C $_{1-4}$ alkyl and/or when R_6 and R_7 are not the same group and/or when ---- is a single bond.

It is to be understood that all stereoisomeric forms, including all enantiomers, diastereoisomers and all mixtures thereof, including racemates, are encompassed within the scope of the present invention and the reference to compounds of formula (I) includes all stereoisomeric forms unless otherwise stated.
Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention.

The present invention also includes isotopically-labeled compounds, which are identical to those recited in formulas I and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I.

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically - labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated , i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium , i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The term C_{1-4} alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl.

The term halogen refers to fluorine, chlorine, bromine or iodine.

The term C_{3-7} cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term C_{1-4} alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, prop-1-oxy, prop-2-oxy, but-1-oxy, but-2-oxy or 2-methylprop-2-oxy.

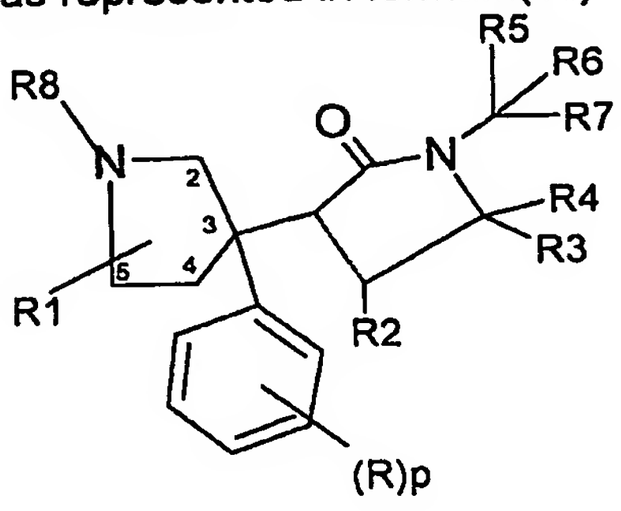
When R_5 is a 5 or 6 membered heteroaryl group according to the invention this includes furanyl, thiophenyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,3-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-oxadiazolyl, 1,2,5-thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,4-oxadiazolyl, 1,2,5-triazinyl or 1,3,5-triazinyl and the like.

The term 9 to 10 membered fused bicyclic heterocyclic group refers to a 5, 6/6, 5 or 6, 6 bicyclic ring system, containing at least one heteroatom selected from oxygen, sulphur or nitrogen, which may be saturated, unsaturated or aromatic. The term 9 to 10 membered fused bicyclic heterocyclic group also refers to a phenyl fused to a 5 or 6 membered heterocyclic group. Example of such groups include benzofuranyl, benzothiophenyl, indolyl, benzoxazolyl, 3H-imidazo[4,5-c]pyridin-yl, dihydrophthazinyl, 1H-imidazo[4,5-c]pyridin-1-yl, imidazo[4,5-b]pyridyl, 1,3-benzo[1,3]dioxolyl, 2H-chromanyl, isochromanyl, 5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyrimidyl, 1,3-benzothiazolyl, 1,4,5,6-tetrahydropyridazyl, 1,2,3,4,7,8-hexahydropteridinyl, 2-thioxo-2,3,6,9-tetrahydro-1H-purin-8-yl, 3,7-dihydro-1H-purin-8-yl, 3,4-dihydropyrimidin-1-yl, 2,3-dihydro-1,4-benzodioxinyl, benzo[1,3]dioxolyl, 2H-chromenyl, chromanyl, 3,4-dihydrophthalazinyl, 2,3-dihydro-1H-indolyl, 1,3-dihydro-2H-isoindol-2-yl, 2,4,7-trioxo-1,2,3,4,7,8-hexahydropteridinyl, thieno[3,2-d]pyrimidinyl, 4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidinyl, 1,3-dimethyl-6-oxo-2-thioxo-2,3,6,9-tetrahydro-1H-purinyl, 1,2-dihydroisoquinolinyl, 2-oxo-1,3-benzoxazolyl, 2,3-dihydro-5H-1,3-thiazolo[3,2-a]pyrimidinyl, 5,6,7,8-tetrahydro-quinazolinyl, 4-oxochromanyl, 1,3-benzothiazolyl, benzimidazolyl, benzotriazolyl, purinyl, furylpyridyl, thiophenylpyrimidyl, thiophenylpyridyl, pyrrolylpiridyl, oxazolylpyridyl, thiazolylpiridyl, 3,4-dihydropyrimidin-1-yl imidazolylpiridyl, quinoliyl, isoquinolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrazolyl[3.4]pyridine, 1,2-dihydroisoquinolinyl, cinnolinyl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 4,5.6,7-tetrahydro-benzo[b]thiophenyl-2-yl, 1,8-naphthyridinyl, 1,6-naphthyridinyl, 3,4-dihydro-2H-1,4-benzothiazine, 4,8-dihydroxy-quinolinyl, 1-oxo-1,2-dihydro-isoquinolinyl or 4-phenyl-[1,2,3]thiadiazolyl and the like.

The term 5 or 6 membered heterocyclic group refers to 5 or 6 ring members containing at least one heteroatom selected from oxygen, sulphur or nitrogen, which may be saturated or unsaturated. Examples of such groups include piperidyl, 2-oxodihydrofuranyl, piperazinyl, morpholinyl, pyrazolidinyl, 1,2 dihydro-3H-pyrazolyl, imidazolidinyl or pyrrolidinyl and the like.

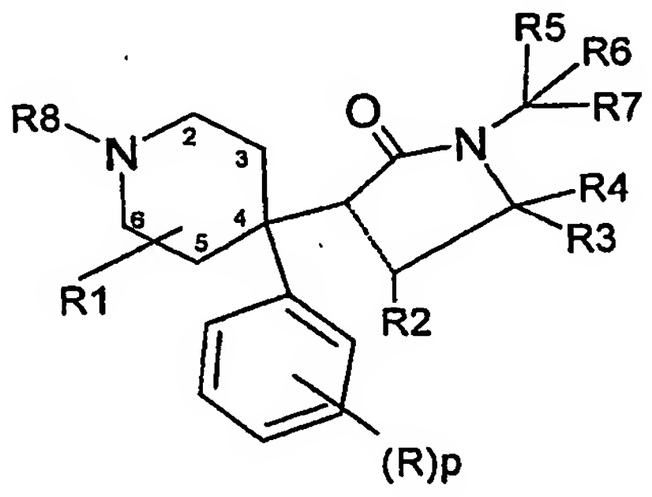
In the compounds of formula (I) wherein n is 1 the group R_1 may be in position 2, 4, or 5

as represented in formula(1c)



(1c)

In the compounds of formula (I) wherein n is 2 the group R_1 may be in position 2, 3, 5 or 6 of the piperidine ring as represented in formula (1d)



(1d)

R is preferably halogen (e.g. fluorine) or methyl.

R_1 is preferably hydrogen, halogen (e.g. fluorine) or methyl.

R_2 is preferably hydrogen or methyl.

R_3 is preferably hydrogen or methyl.

R_4 is preferably hydrogen.

R_5 is preferably phenyl optionally substituted by one group selected from cyano, methyl, chlorine, bromine or fluorine atom or R_5 is preferably naphthyl optionally substituted by one group selected from cyano, methyl, chlorine, bromine or fluorine atom.

R_6 is preferably hydrogen or methyl.

R_7 is preferably hydrogen or methyl.

R_8 is preferably hydrogen or methyl.

n is preferably 2.

p is preferably 0 or 1.

Preferred compounds according to the invention are:
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one;
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one1-[1-(3,5-Dichlorophenyl)ethyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one ;
1-[1-(3,5-Dichlorophenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one;
1-[1-(3-Chloro-1-naphthalenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one;
1-[1-(3-Chloro-1-naphthalenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one;
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-2-pyrrolidinone and enantiomers, diastereoisomers, phamaceutically acceptable salts (e.g hydrochloride, fumarate or citrate) and solvates thereof.

Particular preferred compounds of the invention are
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one;
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one
and amorphous and crystalline forms thereof and phamaceutically acceptable salts (e.g hydrochloride, fumarate or citrate) and solvates thereof.

The compounds of the invention are antagonists of tachykinin receptors, including substance P and other neurokinins, both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

Tachykinins are a family of peptides that share a common carboxyl-terminal sequence (Phe-X-Gly-Leu-Met-NH2). They are actively involved in the physiology of both lower and

advanced lifeforms. In mammalian lifeforms the main tachykinins are subtance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB) which act as neurotransmitters and neuromodulators. Mammalian tachykinins may contribute to the pathophysiology of a number of human diseases.

Three types of tachykinins receptors have been identified, namely NK1(SP-preferring), NK2 (NKA-preferring) and NK3 (NKB-preferring) which are widely distributed throughout the central nervous (CNS) and peripheral nervous system.

Particularly the compounds of the invention are antagonists of the NK1 receptor.

The compounds of the present invention also have activity as selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) and are thus of use in the treatment of conditions mediated by selective inhibition of the serotonin reuptake transporter protein.

Thus, the compounds of the present invention combine dual activity as tachykinin antagonists, including substance P and other neurokinins, and as SSRIs. In particular, the compounds of the invention combine dual activity as NK1 receptor antagonists and as SSRIs.

NK_1-receptor binding affinity has been determined in vitro in a binding Scintillation proximity assay (SPA) by measuring the compounds' ability to displace [^{125}I]Tyr8-Substance P (SP) from recombinant human NK_1 receptors stably expressed in Chinese Hamster Ovary (CHO) cell membranes prepared by using a modification of the method described by Beattie D.T. et al. (Br. J. Pharmacol, 116:3149-3157, 1995). Briefly, polystrene Leadseeker WGA-SPA beads (Amersham Biosciences) were mixed with cell membranes in a bead/membrane ratio of 50:1 (w/w) in assay buffer (75 mM Tris pH 7.8, 75 mM NaCl, 4 mM MnCl2, 1 mM EDTA, 0.05% Chaps, 1 mM PMSF). The mixture was placed on ice for 30 minutes to allow the formation of membrane/bead complex before BSA was added to a final concentration of 1%. After another 30 minutes incubation on ice, the bead/membrane complex was washed twice and suspended in assay buffer. [^{125}I]Tyr8-Substance P (2200 Ci/mmol, PerkinElmer) was then added to the bead/membrane complex with a final concentration of 0.4 nM. 30 ul of the resulting mixture was then dispensed to each well of Nalgen NUNC 384-well plate with 1 ul compound pre-dispensed in DMSO. The plates were then sealed and pulse centrifuged at 1100 rpm. After 3 hours incubation at room temperature with shaking, the plates were centrifuged for 2 min at 1100 rpm and measured in Viewlux imager (PerkinElmer) for 5 minutes with a 618-nm filter. Inhibition of [^{125}I]Tyr8-Substance P binding to NK_1-receptors

was measured by the reduction of luminescent signal. IC_{50} values of each compound were determined by an 11-point 3x-dilution inhibition curve. pK_i values were calculated using the K_D of [^{125}I]Tyr8-Substance P determined in a separate experiment.

For preferred compounds of the invention NK_1-receptor binding affinity has also been determined in vitro using conventional filtration techniques by measuring the compounds' ability to displace [^{3}H] -substance P SP from recombinant human NK_1 receptors expressed in CHO cell membranes prepared as described above.Briefly, ligand binding was performed in 0.2 ml of 50 mM HEPES, pH 7.4, containing 3 mM $MnCl_2$, 0.02% BSA, 0.5 nM [^{3}H]-Substance P (30-56 Ci/mmol Amersham), a final membrane protein concentration of 30-50 µg/ml, and the test compounds. The incubation proceeded at room temperature for 40 min and was stopped by filtration. Non-specific binding was determined using excess of substance P (1 µM) and represents about 6-10% of the total binding.

Preferred compounds of the invention were further characterised in a functional assay for the determination of their effect to inhibit the intracellular calcium increase induced by SP in Human-NK_1-CHO cells using FLIPR technology. Briefly, after 30 minutes incubation with the cytoplasmic calcium indicator Fluo-4 AM (2µM), cells were washed and incubated in the absence or presence of three or more different concentrations of antagonist for 60 minutes, at 37°C in Hank's balanced salts with 20mM Hepes, and then non-cumulative concentration-response curves of SP (2pM-300nM) was performed. The potency of the antagonist (pK_B value) was calculated from Schild's analysis.

The inhibitory activity of the compounds at the human serotonin transporter (hSERT) has been determined in vitro using porcine LLCPK cells (ATCC.) stably transfected with the hSERT (hSERT-LLCPK). The cells have been plated onto 96-well plates (10000 cells/well). After 24 hr, cells have been washed in uptake buffer (Hank's balanced salt solution + 20 mM Hepes) and pre-incubated for 10 minutes at 30°C with 50 µl of buffer containing the test compounds. 50 µl of 50 nM [^{3}H] Serotonin (5-HT) solution (final concentration: 25 nM [^{3}H] 5-HT) have been added and plates have been incubated for 7 min at 30°C, during which cells take up radiolabelled 5-HT. Aspirating the solution and rapidly washing the cells with cold buffer has terminated the uptake.
The amount of radioactive 5-HT incorporated in the cells has then been measured by adding the scintillation cocktail directly onto the cells and reading the plate in the Top Count. The data have been digitally processed to obtain the pIC_{50} values of the uptake inhibitors.

For preferred compounds of the invention hSERT binding affinity has been determined in vitro by the compounds' ability to displace [^{3}H]-citalopram from hSERT-LLCPK cell membranes. For the binding reaction, a final concentrationof 0.25 nM of [^{3}H] citalopram (84 Ci/mmol, Amersham) were incubated with 3-5µg/ml of cell membrane and the compound to be tested at different concentrations (7 concentration points in duplicate) in 50 mM Tris HCl, pH 7.7, containing 120 mM NaCl , 5 mM KCl, 10µM pargyline and 0.1% ascorbic acid. The reaction was performed for 120 min at 22°C and was terminated through GF/B Unifilter (pre-soaked in 0.5 % PEI) using a Cell Harvester (Tomtec). Scintillation fluid was added to each filtered spot and radioactivity was determined using a scintillation counter (TopCount (Packard)). Non-specific binding was determined using paroxetine (10µM) and represents about 2-5% of the total binding.

Msat601 software package was used to elaborate the competition binding data.
IC_{50} values were converted to pK_i values using the Cheng-Prusoff equation and by using the K_D of [^{3}H]citalopram determined in a separate experiment.

The action of the compounds of the invention at the NK_1 receptor and/or serotonin transporter may be determined by using conventional animal models.
Thus, the ability to bind at the NK_1 receptor and/or serotonin transporter was determined using the guinea pig pup isolation calls model as described by Pettijohn, Psychol. Rep., 1979 and Rupniak et al., Neuropharmacology, 2000.
The anti-anxiety activity obtained by the administration of a compound according to the invention can be demonstrated in the gerbil social interaction model, according to the method described by Cheeta et al. (Cheeta S. et al., 2001. Brain Research 915: 170-175).

Compounds of the invention are useful in the treatment of CNS disorders and psychotic disorders, in particular in the treatment or prevention of depressive states and/or in the treatment of anxiety as defined in, but not restricted to, Diagnostic Statistical of Mental Disorder (DSM) IV edition edit by American Psychiatric Association and International Classification Diseases 10th revision (ICD10).
Thus, for example, depressive states include Major Depressive Disorders (MDD), including bipolar depression, unipolar depression, single or recurrent major depressive episodes, recurrent brief depression, with or without psychotic features, catatonic

features, melancholic features including anorexia, weight loss, atypical features, anxious depression, cyclothymic or postpartum onset.

Other mood disorders encompassed within the term major depressive disorders include dysthymic disorders with early or late onset and with or without atypical features, neurotic depression, post-traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

The term anxiety includes anxiety disorders, such as panic disorders with or without agoraphobia, agoraphobia phobias, for example, social phobias or specific phobia agoraphobia, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorders, generalised anxiety disorders, acute stress disorders and mixed anxiety-depression disorders.

Compounds of the invention are useful as analgesics. In particular, they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of the cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore, compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds) or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of addiction to cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof.

Compounds of the invention are also useful as anti-inflammatory agents. In particular, they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment or prevention of schizophrenic disorders including paranoid schizophrenia, disorganised schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, residual schizophrenia.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin,

mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5-fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease (GERD) such as erosive GERD and symptomatic GERD or non erosive GERD, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn, dyspepsia and functional dyspepsia.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome, gastro-oesophageal reflux disease (GERD) such as erosive GERD and symptomatic GERD or non erosive GERD, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn, dyspepsia and functional dyspepsia (such as ulcer-like dyspepsia, dysmotility-like dyspepsia and unspecified dyspepsia) chronic constipation; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

The compounds of the invention are also useful in premenstrual dysphoric disorder (PMDD), in chronic fatigue syndrome and Multiple sclerosis.

Compounds of the invention have been found to exhibit anxiolytic and antidepressant activity in conventional tests. For example, in Guinea pig pups separation-induced vocalisations (Molewijk et al., 1996) and in the gerbil social interaction model, according to the method described by Cheeta et al. (Cheeta S. et al., 2001. Brain Research 915: 170-175).

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of serotonin reuptake.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

In a further aspect there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of depression and /or anxiety.

In a further aspect there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the use in the treatment of depression and/or anxiety.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention is provided a method for the treatment of a mammal, including man, in particular for the treatment of depression and/or anxiety which method comprises administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus, compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

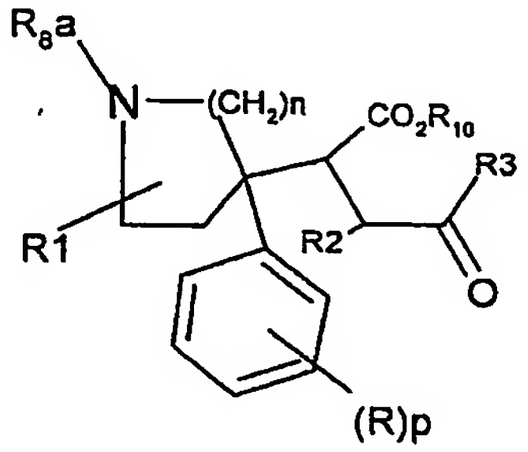
For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be

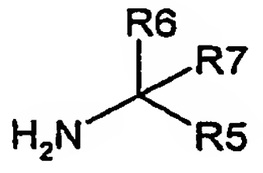
ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.
Thus, for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 300 mg e.g. 1 to 100 mg.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1,R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, n, p, q and r have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (I), wherein ---- is a single bond, R_3 represents hydrogen or C_{1-4} alkyl and R_4 represents hydrogen, may be prepared by reductive N-alkylation of a compound of formula (II),

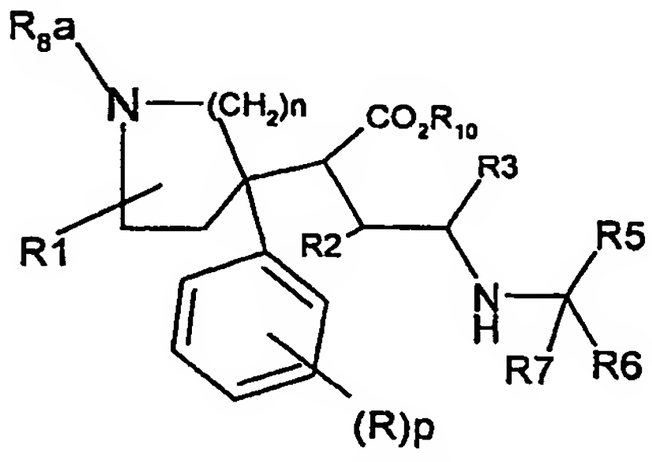


(II)



(III)

in which R_{10} is methyl or ethyl, R_3 is hydrogen or C_{1-4} alkyl and R_{8a} has the meaning defined in formula (I) or is a nitrogen protecting group, with the amine (III) to form an amino derivative (IV),

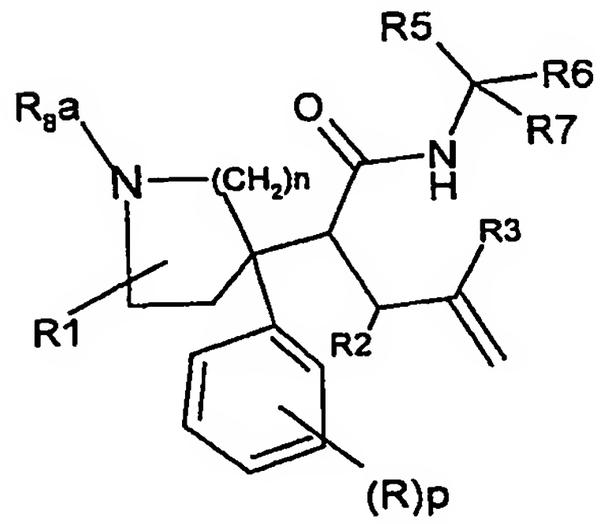


(IV)

followed by cyclisation reaction in the presence of an alkali metal base e.g. sodium methoxy and where necessary followed by removal of the nitrogen protecting group.
The reductive N-alkylation may be carried out in an aprotic solvent such as dichloroethane or acetonitrile and in the presence of a suitable metal reducing agent such as sodium borohydride or sodium triacetoxyborohydride.

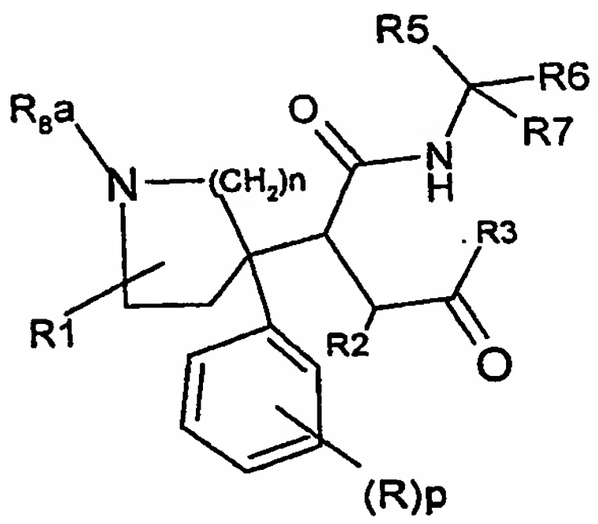
The cyclisation reaction is conveniently carried out in a solvent such as an alkanol e.g. methanol or ethanol at temperature within the range 20° to 60°C.
If desired, compounds of formula (IV) may be isolated before the cyclisation reaction takes place.

Compounds of formula (I), wherein ---- is a single bond, R_3 is hydroxy and R_4 is hydrogen, may be prepared by oxidation of an allyl derivative of formula (V),



(V)

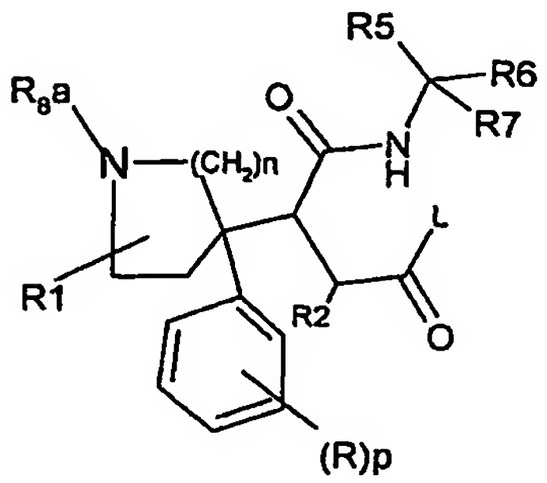
in which R_{8a} is defined as in formula (II) and R_3 is hydrogen, to form the aldehyde (VI), followed by in situ cyclisation thereof and where necessary followed by removal of the nitrogen protecting group.



(VI)

The oxidation may be carried out using conventional oxidasing agents known in the art for converting an allyl group into a carbonyl group.
Thus, for example, the oxidation to form aldehyde is conveniently carried out using osmium tetroxide followed by reaction with sodium periodate in water miscibile solvents (e.g tetrahydrofuran) and water preferably at room temperature.
The cyclisation may be carried out by stirring the above mixture overnight at room temperature.
If desired, compounds of formula (VI) may be isolated before the cyclisation takes place.

Compounds of formula (I), wherein --- is a single bond and R_3 together with R_4 represents =O, may be prepared by cyclisation of a compound of formula (VII),



(VII)

wherein R_{8a} is defined as in formula (II) and L is a suitable leaving group such as for example alkoxy (e.g methoxy or ethoxy).

The cyclisation reaction is conveniently carried out in the presence of an organic base such as NaH and in an aprotic solvent such as THF and at a temperature ranging from 0^oC to 80^oC.

Compounds of formula (I), wherein ----is a double bond, R_3 represents hydrogen or C_{1-4} alkyl and R_4 is hydrogen, may be prepared by cyclisation of a compound of formula (VI) in which R_3 represents hydrogen or C_{1-4} alkyl and R_{8a} is defined as in formula (I) or is a nitrogen protecting group, in the presence of a strong acid such as sulfuric acid, trifluoro acetic , hydrochloric acid or p-toluensulfonic acid.The reaction is conveniently carried out by heating at temperature between 20°-80° C.

Alternatively, formula (I), wherein ----is a double bond, R_3 represents hydrogen or C_{1-4} alkyl and R_4 is hydrogen, may be prepared by oxidation of a compound of formula (V) using the condition described above for preparing compounds (VI) followed by cyclisation with a strong acid as above described without isolating compounds of formula (VI).

Alternatively, formula (I), wherein ----is a double bond, R_3 represents hydrogen and R_4 is hydrogen, may be prepared by reaction of a compound of formula(I) wherein ----- is a single bond, R_3 represents hydroxy, R_8 has the meaning defined in formula (I) or is a nitrogen protecting group, with a strong acid as sulfuric acid, trifluoro acetic , hydrochloric acid or p-toluensulfonic acid .

Compounds of formula (I) wherein ---- is a double bond and R_3 is hydroxy or R_3 together with R_4 represents =O may be prepared by reaction of a compound of formula (I) wherein ----- is a single bond, R_8 has the meaning defined in formula (I) or is a nitrogen protecting

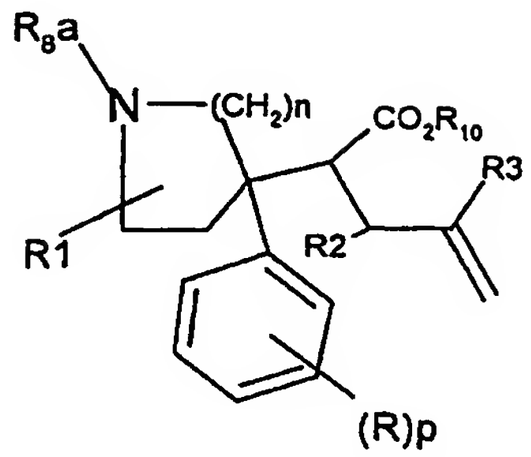
group and R_3 is hydroxy protected group or R_3 together with R_4 represents =O, with a suitable brominating agent followed by treatment with a base such as sodium ethoxide or methoxide and by removal of any protecting group.
A suitable brominating agent to be used in this reaction is N-bromosuccinimide.

In a further embodiment compounds of formula(I), wherein R_8 is $(CH_2)rR_9$ wherein r is an integer from 1 to 4 , may be prepared by reductive alkylation of a compound of formula(I), wherein R_8 is hydrogen, with an aldehyde, $CH(O)(CH_2)_mR_9$ (VIII), wherein m is an integer from 0 to 3 The reductive N-alkylation may be carried out in an aprotic solvent such as dichloroethane or acetonitrile and in the presence of a suitable metal reducing agent such as sodium borohydride or sodium triacetoxyborohydride.
In a further embodiment compounds of formula(I), wherein R_8 is $(CH_2)rR_9$ wherein r is 0 and R_9 is C_{3-7} cycloalkyl, may be prepared by alkylation of a compound of formula (I), wherein R_8 is hydrogen with a compound L- R_9 (IX), wherein L is a suitable leaving group such as halogen (e.g iodine, chlorine or bromide).
The reaction is conveniently carried out in a solvent such as NN-dimethylformamide or tetrahydrofuran.

When R_{8a} is a nitrogen protecting group, examples of suitable groups include alkoxycarbonyl e.g. t-butoxycarbonyl, benzyloxycarbonyl, arylsulphonyl e.g. phenysulphonyl or 2-trimethylsilylethoxymethyl.
Protection and deprotection may be effected using conventional techniques such as those described in "Protective Groups in Organic Synthesis 3rd Ed." by T.W. Greene and P. G. M. Wuts (John Wiley and Sons, 1999) and as described in the examples hereinafter.

Examples of suitable hydroxy protecting reagents include acetic anhydride, benzoic anhydride or a trialkylsilyl chloride in an aprotic solvent. Examples of aprotic solvent are dichloromethane, NN-dimethylformamide, dimethylsulfoxide, tetrahydrofuran and the like.
The hydroxyl protecting groups may be removed by well known standard procedures.

Compounds of formula(II) may be prepared by oxidation of a compound of formula (X), wherein R_{8a} and R_{10} have the meaning defined as in formula (II).

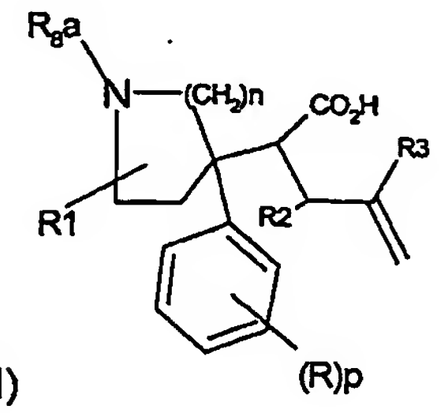


(X)

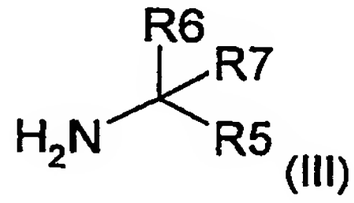
The oxidation is conveniently carried out in the presence of osmium tetroxide followed by reaction with sodium periodate.

The reaction is carried out in a solvent such as N,N dimethylformamide or tetrahydrofuran.

Compounds of formula (V) may be prepared by reaction of a compound of formula (X), wherein R_{8a} and R_{10} have the meaning defined in formula(II), with a strong base such as lithium hydroxide or sodium hydroxide to obtain a carboxylic acid of formula (XI) followed by reaction of an activated derivative thereof with a compound of formula (III)



(XI)



(III)

followed where necessary by removal of any nitrogen protecting group.

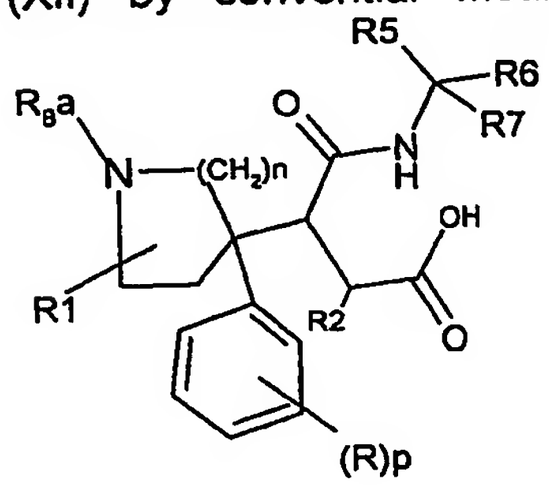
Suitable activated derivatives of the carboxyl group include the acyl halide, mixed anhydride, activated ester such as thioester or the derivative formed between the carboxylic acid group and a coupling agent such as that used in peptide chemistry, for example carbonyl diimidazole, O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate or dicyclohexylcarbodiimide.

The reaction is preferably carried out in an aprotic solvent such as hydrocarbon, halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran, NN-dimethylformamide.

The activated derivatives of the carboxylic acid (X) may be prepared by conventional means. A particular suitable activated derivative for use in this reaction is O-(benzotriazol-1-yl) –N,N,N',N'-tetramethyluronium tetrafluoroborate.

The reaction is suitably carried out in a solvent such as NN-dimethylformamide.

Compounds of formula (VII) may be prepared from the corresponding carboxy derivative (XII) by convential means for converting carboxylic groups into leaving groups.

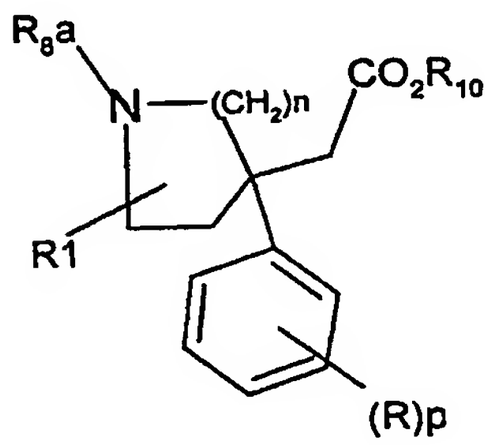


(XII)

Thus, for example, a compound of formula (VII) in which L is a chlorine atom may be prepared by treating a compound of formula (XII) with thionyl chloride in an aprotic solvent such as tetrahydrofuran and optionally in the presence of a tertiary organic base.

Compounds of formula (XII) may be prepared by oxidation of a compound of formula (V). The oxidation may be carried out using conventional oxidasing agents known in the art for converting an allyl group into a carboxyl group,using for example manganese dioxide.

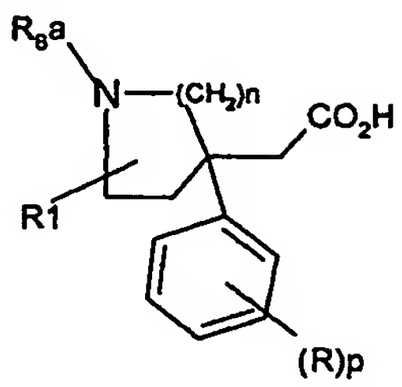
Compounds of formula (X) may be prepared by reaction of a compound of formula (XIII),



(XIII)

wherein R_{8a} and R_{10} have the meaning defined as in formula (II), with an allyl derivative CH2=C(R3)HC(R2)L (XIV) wherein L is a suitable leaving group such as halogen such as iodine, bromide.

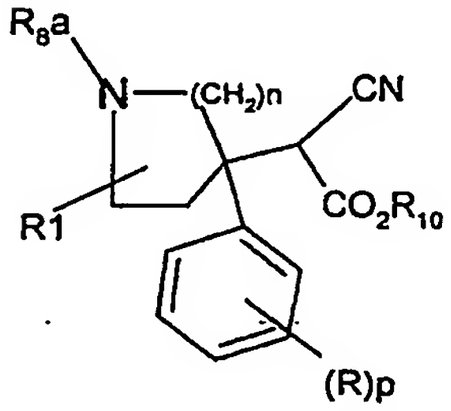
Compounds of formula (XIII) may be prepared by reaction of activated derivative of compounds of formula (XIV), wherein R_{8a} has the meaning defined as in formula (II), with methanol or ethanol.



(XIV)

A particular suitable activated derivative for use in this reaction is O-(benzotriazol-1-yl) – N,N,N',N'-tetramethyluronium tetrafluoroborate.

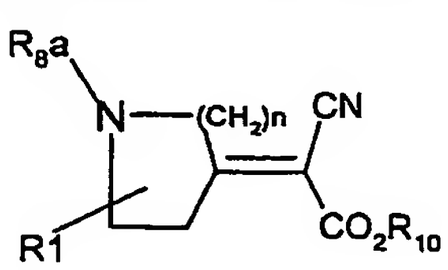
Compounds of formula (XIV) may be preprared from cyano derivative (XV),



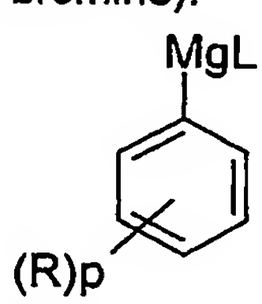
(XV)

wherein R_{8a} and R_{10} have the meaning defined as in formula (II), by reaction with an acid, such as for example concentrated sulfuric acid.The reaction is conveniently carried out in a solvent such as acetic acid in the presence of water and heating the reaction mixture up to 150°C

Compounds of formula (XV) may be prepared by reaction of a compound of formula (XVI), wherein R_{8a} and R_{10} have the meaning defined in formula (II), with a compound of formula (XVII) , wherein L is a suitable halogen (i.e bromine).



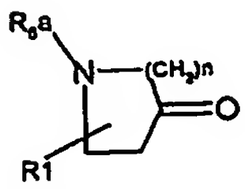
(XVI)



(XVII)

The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon (e.g. toluene), ethers (e.g. tetrahydrofuran) and at a temperature within the range 0-25°C, optionally in the presence of cupper(I) salts such as for example cupper iodide.

Compounds of formula (XVI) may be prepared by reaction of a compounds of formula (XVIII) with a cyano derivative (XIX).



(XVIII)

$CNCH_2CO_2R_{10}$ (XIX

Ammine of formula (III) and compounds of formulae (XIX) and (XVIII) are commercially available compounds or may be prepared by analogous methods to those used for known compounds. Thus compounds of formula (XVIII) may be prepared according to the procedure described in WO 2001/000206.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.

Thus, for example, specific enantiomers of the compounds of formula (I) may be obtained from the corresponding enantiomeric mixture of a compound of formula (I) using chiral HPLC procedure.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Thus, in a one embodiment of the invention the enantiomers of the compound of formula (I) may be prepared by reaction of a chiral amine (III) using any of the processes described above for preparing compounds of formula (I) from amine (III).

The chiral amine (III) may be prepared from the corresponding racemic amine (III) using any conventional procedures such as salt formation with a suitable optically active acid such as for example di-p-toluoyl-D-tartaric acid, (*S*)-methoxyphenylacetic acid or di-p-toluoyl-L-tartaric acid, or using chiral HPLC procedure.

Where it is desired to isolate a compound of formula (I) as a salt, for example a pharmaceutically acceptable salt, this may be achieved by reacting a compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether, *tert*-butylmethyl ether or tetrahydrofuran).

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined by DSC. R.T. or r.t. refer to room temperature.

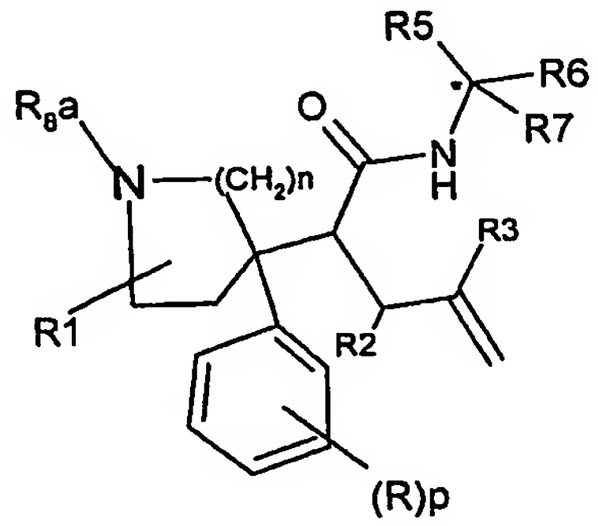
Infrared spectra (IR) were measured in chloroform or nujol solutions on a FT-IR instrument. Proton Magnetic Resonance (NMR) spectra were recorded on Varian instruments at 300, 400 or 500 MHz, on Bruker instrument at 300 MHz, chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, double; t, triple; q, quartet; m, multiplet; b, broad.

The NMR spectra were recorded at temperature ranging from 25 to 90°C; when more than one conformer were detected the chemical shifts for the most abundant one is reported. Mass spectra (MS) were taken on a 4 II triple quadrupole Mass Spectrometer (Micromass UK) and on a Agilent MSD 1100 Mass Spectrometer, operating in ES (+) and ES (-) ionization mode. In the mass spectra only one peak in the molecular ion cluster is reported. Optical rotations were determined at 20°C with a Jasco DIP360 instrument (l=10 cm, cell volume = 1 mL, λ = 589 nm). Flash silica gel chromatography was carried out over silica gel 230-400 mesh supplied by Merck AG Darmstadt, Germany or over Varian Mega Be-Si pre-packed cartridges or over pre-packed Biotage silica cartridges. The X-ray powder diffraction pattern of a crystalline form of the compounds of the invention was obtained by loading the sample into the diffractometer (Siemens D5005 X-ray diffractometer equipped with θ/θ goniometer, scintillation counter and graphite monochromator. The diffractometer was set up with the instrumental parameters given below:

Monochromatic radiation: Cu - 1.54056/1.54439
θrange 2: 2°-40° 2θ
Generator voltage/current: 40kV/50mA
Step size: 0.02° 2θ
Time per step: 2 sec-1
Rotation: on
Divergence/Antiscattering slit: variable
Sample holder: round cavity on low-background plate.
The spectrum obtained was analysed using the data evaluation software EVA 7.0.

T.l.c. refers to thin layer chromatography on 0.25 mm silica gel plates (60F-254 Merck) and visualized with UV light. For phase separations performed by using microfiltration devices: phase separation cartridge with polypropylene frit by Whatman or Alltech. SCX means: SCX-cartridges (loading 0.75mmol\g) by Varian.
Solutions were dried over anhydrous sodium sulphate.
Methylene chloride was redistilled over calcium hydride and tetrahydrofuran was redistilled over sodium.
The following abbreviations are used in the text: AcOEt = ethyl acetate, CH = cyclohexane, DCM = methylene chloride, DIPEA = N,N-diisopropylethylamine, DMF = N,N'-dimethylformamide, Et2O = diethyl ether, EtOH = ethanol, MeOH = methanol, TEA = triethylamine, THF = tetrahydrofuran, TFA = trifluoroacetic acid, CH3CN= acetonitrile, TBTU = O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate.
Enantiomer 1 or enantiomer 2 means a compound of the invention or an intermediate thereof as a single enantiomer whose configuration was not determined.

Isomer 1 or Isomer 2 means a mixture of diastereoisomers wherein the configuration at the chiral center (namely the carbon atom shown as * in formula (A) is fixed but was not determined.



(A)

Intermediate 1

[1-(3,5-Dichlorophenyl)ethyl]amine

A solution of 3,5-dichlorobenzaldehyde (54.3 g) in dry THF (300 mL) was added dropwise to lithium bis(trimethylsilyl)-amide (1M solution in THF - 340 mL) at -30°C under a Nitrogen atmosphere. The resulting orange mixture was allowed to warm to – 5°C under stirring in a Nitrogen atmosphere in 1 hour, then it was cooled down to -60°C and methyllithium (1.6M solution in Et2O - 290 mL) was added keeping the internal temperature of the reaction mixture < -55°C.

The resulting dark violet reaction mixture was stirred for 1 hour at -60°C under a Nitrogen atmosphere, then it was carefully quenched at -60°C with 2N hydrochloric acid solution (20 mL) followed by 6N hydrochloric acid solution to pH = 2. The reaction mixture was concentrated *in vacuo* and the aqueous residue was washed with 1:1 CH/Et2O (500 mL). The separated aqueous phase was then made basic (pH = 14) at 0°C with NaOH pellets. The basic aqueous phase was extracted with Et2O (4 x 400 mL), the collected organic layers were dried and concentrated *in vacuo* to give the title compound (60 g) as a yellow oil.

T.l.c.: DCM/MeOH 9:1, Rf=0.5 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.25 – 7.15 (m, 3H); 4.05 (q, 1H); 1.35 (d, 3H).

MS (ES/+): m/z= 190 $[M+H]^+$.

Intermediate 2 and Intermediate 3

[1-(3,5-Dichlorophenyl)ethyl]amine (enantiomer 1) and [1-(3,5-dichlorophenyl)ethyl]amine (enantiomer 2)

A solution of (*S*)-methoxyphenylacetic acid (23 g) in acetone (140 mL) was added to a solution of intermediate **1** (25 g) in acetone (140 mL). The thick suspension was heated at 56°C for 1 hour then it was stirred at r.t. overnight. The slurry was filtered and the solid residue washed with acetone (200 mL). The solid (47 g) was triturated in acetone (500 mL) by heating to reflux for 1 hour, cooling to r.t. and stirring overnight. The suspension

was filtered and the solid residue (29 g) washed with acetone (500 mL) and triturated three times as described above to give (*S*)-methoxyphenylacetic acid salt of [1-(3,5-dichloro-phenyl)-ethyl]amine (16.6 g). The solid was stirred in a mixture of saturated sodium hydrogen carbonate solution (200 mL) and DCM (200 mL). The organic phase was separated, washed with brine (200 mL), dried and concentrated *in vacuo* to give the title compound intermediate **2** (8.2 g) as a colourless oil.

The same procedure was performed on a distinct batch of intermediate **1** (7.5 g) to obtain the title compound intermediate **2** (1.6 g); the mother liquors from the precipitation were evaporated *in vacuo* to give a residue (9.5 g), which was treated with saturated sodium hydrogen carbonate solution (50 mL) and extracted with DCM (50 mL). The colourless oil thus obtained (5 g) was treated with (*R*)-methoxyphenylacetic acid (4.3 g) in acetone as described above (one precipitation and two triturations) to give (*R*)-methoxyphenylacetic acid salt of [1-(3,5-dichloro-phenyl)-ethyl]amine (3.26 g). The solid was stirred in a mixture of saturated sodium hydrogen carbonate solution (50 mL) and DCM (50 mL). The organic phase was washed with brine (50 mL), dried and concentrated *in vacuo* to give the title compound intermediate **3** (1.6 g) as colourless oil.

Intermediate 2: (enantiomer 1)

NMR ($CDCl_3$): δ (ppm) 7.25 – 7.15 (m, 3H); 4.05 (q, 1H); 1.35 (d, 3H).
MS (ES/+): m/z= 190 $[M+H]^+$.
HPLC (column: Chiral-AGP 15cm x 2mm, 5µm; injection volume=1µL; mobile phase: ammonium phosphate buffer 100mM pH=4.4 / MeOH isocratic 99/1 % v/v; flow rate= 0.13 mL/min; detection: λ=210 nm): retention time = 5.4 minutes; purity (a/a %) >98%.

Intermediate 3: (enantiomer 2)

NMR ($CDCl_3$): δ (ppm) 7.25 – 7.15 (m, 3H); 4.05 (q, 1H); 1.35 (d, 3H).
MS (ES/+): m/z= 190 $[M+H]^+$.
HPLC (column: Chiral-AGP 15cm x 2mm, 5µm; injection volume=1µL; mobile phase: ammonium phosphate buffer 100mM pH=4.4 / MeOH isocratic 99/1 % v/v; flow rate= 0.13 mL/min; detection: λ=210 nm): retention time = 6.2 minutes; purity (a/a %) >99%.

Intermediate 4

[1-(3-Chloro-1-naphthalenyl)ethyl]amine

A solution of 3-chloro-naphthalenecarbaldehyde (1.93 g) in dry THF (12 mL) was added dropwise to lithium bis(trimethylsilyl)-amide (1M solution in THF - 10.1 mL) at -30°C under a Nitrogen atmosphere. The resulting yellow mixture was stirred under a Nitrogen atmosphere from -30°C to -5°C for 1 hour, then it was cooled down to -60°C and methyllithium (1.6M solution in Et2O - 11 mL) was added keeping the internal temperature of the reaction mixture < -55°C.

The resulting dark violet reaction mixture was stirred for 40 minutes at -50°C under a Nitrogen atmosphere, then it was carefully quenched at -50°C with 2N hydrochloric acid solution (30 mL) until pH = 2. The reaction was concentrated *in vacuo* and the aqueous residue was washed with 1:1 CH/Et2O (50 mL). The separated aqueous phase was then

made basic (pH = 14) at 0°C with NaOH pellets. This basic aqueous phase was extracted with Et2O (3 x 60 mL), the collected organic layers were dried and concentrated *in vacuo* to give the title compound (1.12 g) as a yellow oil.
T.l.c.: AcOEt/MeOH 8:2, Rf=0.25 (detection with ninhydrine).
NMR (d_6-DMSO): δ (ppm) 8.14 (dd, 1H); 7.94 – 7.85 (m, 2H); 7.73 (d, 1H); 7.58 – 7.50 (m, 2H); 4.80 (q, 1H); 1.35 (d, 3H).
MS (ES/+): m/z= 189 $[M-NH_2]^+$.

Intermediate 5 and Intermediate 6

[1-(3-Chloro-1-naphthalenyl)ethyl]amine (enantiomer 2) [1-(3-chloro-1-naphthalenyl)ethyl]amineenantiomer 1)

To a solution of intermediate **4** (1.12 g) in acetone (10 mL), a solution of (*S*)-methoxyphenylacetic acid (0.9 g) in acetone (10 mL) was added. The thick suspension was heated at 56°C for 40 minutes then it was stirred at r.t. overnight. The slurry was filtered and the solid residue washed with acetone (10 mL). The solid (0.87 g) was triturated in acetone (10 mL) by heating to reflux for 1 hour, cooling to r.t. and stirring overnight. The suspension was filtered and the solid residue (0.6 g) washed with acetone (10 mL) and triturated once again as described above to give (*S*)-methoxyphenylacetic acid salt of [1-(3-chloro-naphthalen-1-yl)-ethyl]amine (0.45 g). The solid was stirred in a mixture of saturated sodium hydrogen carbonate solution (20 mL) and DCM (20 mL). The organic phase was washed with brine (20 mL), dried and concentrated *in vacuo* to give the title compound intermediate **5** (0.25 g) as a colourless oil.
The mother liquors from the precipitation and first trituration were collected, concentrated *in vacuo*, treated with saturated sodium hydrogen carbonate solution (20 mL) and extracted with DCM (20 mL). The colourless oil thus obtained (1 g) was treated with (*R*)-methoxyphenylacetic acid (0.8 g) in acetone (8 mL) as described above (one precipitation and two triturations) to give (*R*)-methoxyphenylacetic acid salt of 1-(3-chloro-naphthalen-1-yl)-ethylamine (0.43 g). A portion of this solid (200 mg) was stirred in a mixture of saturated sodium hydrogen carbonate solution (10 mL) and DCM (10 mL). The organic phase was washed with brine (20 mL), dried and concentrated *in vacuo* to give the title compound intermediate **6** (0.100 g) as colourless oil.

Intermediate 5: (enantiomer 2)

NMR (d_6-DMSO): δ (ppm) 8.14 (dd, 1H); 7.94 – 7.85 (m, 2H); 7.73 (d, 1H); 7.58 – 7.50 (m, 2H); 4.80 (q, 1H); 1.35 (d, 3H).
MS (ES/+): m/z=189 $[M-NH_2]^+$.
SFC (Gilson) analytical conditions: column: Chiralcel OD 25 x 4.6mm; mobile phase: CO_2 / Ethanol + 0.1% Isopropanol 92/8 v/v; flow rate= 2.5 mL/min; P = 180 bar; T = 35°C; detection: λ=225 nm): retention time = 13.8 minutes; purity (a/a %) >99%.

Intermediate 6: (enantiomer 1)

NMR (d_6-DMSO): δ (ppm) 8.14 (dd, 1H); 7.94 – 7.85 (m, 2H); 7.73 (d, 1H); 7.58 – 7.50 (m, 2H); 4.80 (q, 1H); 1.35 (d, 3H).
MS (ES/+): m/z=189 $[M-NH_2]^+$.
SFC (Gilson) analytical conditions: column: Chiralcel OD 25 x 4.6mm; mobile phase: CO_2 / Ethanol + 0.1% Isopropanol 92/8 v/v; flow rate= 2.5 mL/min; P = 180 bar; T = 35°C; detection: λ=225 nm): retention time = 12.4 minutes; purity (a/a %) >99%.

Intermediate 7
4-[(1-Cyano-1-ethoxycarbonyl)-methylene]-piperidine-1-carboxylic acid *tert*-butyl ester

Ethyl cyanoacetate (13.9 mL), ammonium acetate (4.64 g) and acetic acid (6.9 mL) were added, under a Nitrogen atmosphere, to a solution of 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (20 g) in anhydrous toluene (200 mL) in a round bottom flask equipped with a Dean Stark apparatus. The mixture was heated to 110°C for 2 hours, then to 85°C overnight and finally to 130°C for 4 hours. The mixture was allowed to cool to r.t. and washed with 1M sodium hydroxide solution, water and brine. The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (15.54 g) as a yellow oil.
T.l.c.: CH/AcOEt 8:2, Rf=0.35 (detection with ninhydrine).
IR (nujol, cm^{-1}): 2229 (C≡N), 1720 and 1694 (C=O).
NMR ($CDCl_3$): δ (ppm) 4.29 (q, 2H); 3.61 (t, 2H); 3.55 (t, 2H); 3.13 (t, 2H); 2.78 (t, 2H); 1.49 (s, 9H); 1.36 (t, 3H).
MS (ES/+): m/z=295 $[M+H]^+$.

Intermediate 8
4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of 4-fluorophenyl magnesium bromide (1.0M in THF, 49 mL) was added dropwise to a mixture of intermediate **7** (8 g) and copper iodide (1.57 g) in anhydrous THF (65 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred under these conditions for 1 hour and then allowed to warm to r.t. and stirred at 23°C for 2 hours. The mixture was cooled to 0°C, treated with 3M hydrochloric acid solution until pH=5 and extracted with AcOEt (3 x 100 mL). The combined organic extracts were washed with a saturated ammonium chloride solution (200 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 85:15) to give the title compound (9.8 g) as a yellow oil.
T.l.c.: CH/AcOEt 6:4, Rf=0.35 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 7.31 (dd, 2H); 7.06 (t, 2H); 3.95 (q, 2H); 3.87 (bs, 2H); 3.54 (t, 1H); 2.85 (bt, 2H); 2.53 (dt, 2H); 1.9 (m, 2H); 1.4 (s, 9H); 1.02 (t, 3H).
MS (ES/+): m/z=391 $[M+H]^+$.

Intermediate 9

4-Carboxymethyl-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate **8** (0.448 g) in acetic acid (2 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C overnight. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (50 mL). Then, di-tert-butyl-dicarbonate (500 mg) was added and the resulting mixture was stirred at r.t. for 5 hours. It was cooled to 0°C and treated with 6N hydrochloric acid solution until pH=3-4 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (210 mg) as a pale yellow foam.

T.l.c.: CH/AcOEt 1:1, Rf=0.25 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 11.78 (bs, 1H); 7.4 (dd, 2H); 7.15 (t, 2H); 3.45 (m, 2H); 3.11 (m, 2H); 2.54 (s, 2H); 2.04 (m, 2H); 1.89 (m, 2H); 1.37 (s, 9H).

MS (ES/-): m/z=336 $[M-H]^-$.

Intermediate 10

1,1-Dimethylethyl 4-(4-fluorophenyl)-4-[2-(methyloxy)-2-oxoethyl]-1-piperidinecarboxylate

To a solution of intermediate **9** (20 g) in dry DCM (250 mL) under a Nitrogen atmosphere at r.t., DIPEA (26 mL) and TBTU (20.9 g) were added. The mixture was stirred at r.t. for 40 minutes, then dry MeOH (10 mL) was added and the brown dark mixture was stirred at r.t. for 14 hours.

The reaction mixture was diluted with DCM (200 mL) and washed with aqueous 5% sodium hydrogen carbonate solution (2 x 250 mL) and then with brine (250 mL); the organic phase was dried, concentrated *in vacuo* to give the title compound (28.6 g) as a brown dark oil which was used without any further purification in the next reaction.

T.l.c.: CH/AcOEt 1:1, Rf=0.72 (detection with ninhydrine).

MS (ES/+): m/z = 374 $[M+Na]^+$.

Intermediate 11

1,1-Dimethylethyl 4-(4-fluorophenyl)-4-{1-[(methyloxy)carbonyl]-3-buten-1-yl}-1-piperidinecarboxylate

To a solution of crude intermediate **10** (38.7 g) in dry THF (300 mL) at -60°C and under a Nitrogen atmosphere, lithium bis(trimethylsilyl)-amide (1M solution in THF -120 mL) was added dropwise. The resulting mixture was warmed up to –15°C and stirred at that temperature for 2 hours, then cooled again to -60°C for the addition of allylbromide (11 mL). The reaction mixture was allowed to warm to r.t. and stirred for 3 hours. The reaction mixture was quenched at 5°C with water (25 ml), THF was evaporated *in vacuo* and the residue oil was dissolved in Et2O (400 mL) and washed with saturated NH_4Cl solution (300 mL) and then with brine (2 x 200 mL). The organic phase was dried, concentrated *in vacuo* and the brown dark oil residue (38.5 g) was purified by flash chromatography (Biotage Flash 75L, CH/AcOEt 9:1). The title compound was obtained as a yellow oil (26 g).

T.l.c.: CH/AcOEt 8:2, Rf=0.39 (detection with ninhydrine).
MS (ES/+): m/z = 414 $[M+Na]^+$.

Intermediate 12

2-[1-{[(1,1-Dimethylethyl)oxy]carbonyl}-4-(4-fluorophenyl)-4-piperidinyl]-4-pentenoic acid

To a solution of intermediate **11** (38.7 g) in isopropanol (200 mL) was added an aqueous lithium hydroxide solution (25 g in 200 mL). The resulting suspension was refluxed for 24 hours, further lithium hydroxide (12.5 g in 100 mL of water) was added and the suspension refluxed for further 48 hours.
Isopropanol was evaporated in vacuo and the basic aqueous phase (pH = 14) was extracted with Et2O (2 x 300 mL). The aqueous phase was acidified at 0°C with 5N hydrochloric acid solution (230 mL) until pH= 4.5. The acidic aqueous phase was then extracted with AcOEt (3 x 600 mL); the collected organic phases were dried and concentrated *in vacuo* to give the title compound (29 g) as a white solid.
T.l.c.: CH/AcOEt 8:2, Rf=0.06 (detection with ninhydrine).
MS (ES/+): m/z = 400 $[M+Na]^+$
MS (ES/-): m/z = 376 $[M-H]^-$.

Intermediate 13

1,1-Dimethylethyl 4-[1-({[(3,5-dichlorophenyl)methyl]amino}carbonyl)-3-buten-1-yl]-4-(4-fluorophenyl)-1-piperidinecarboxylate

To a solution of intermediate **12** (29 g) in dry DMF (280 mL), DIPEA (33 mL) and TBTU (27.1 g) were added, the solution became dark and after 45 minutes of stirring at r.t., 3,5-dichlorobenzylamine (14.2 g) was added; the reaction mixture turned to orange; it was stirred for 1 hour at r.t. under a Nitrogen atmosphere then it was diluted with AcOEt (800 mL) and washed with ice/water 1/1 (4 x 400 mL). The organic phase was dried and concentrated *in vacuo* to give the crude title compound (38.8 g) as a pale orange foam. This material was purified by flash chromatography (Biotage Flash 75L, CH/AcOEt 85:15) to obtain the title compound (38.6 g) as a white foam.
T.l.c.: CH/AcOEt 7:3, Rf=0.45 (detection with ninhydrine).
MS (ES/+): m/z=557 $[M+Na]^+$.

Intermediate 14

1,1-Dimethylethyl 4-[1-({[1-(3,5-dichlorophenyl)ethyl]amino}carbonyl)-3-buten-1-yl]-4-(4-fluorophenyl)-1-piperidinecarboxylate (isomer 1)

DIPEA (0.7 mL) and TBTU (0.835 g) were added to a solution of intermediate **12** (0.77 g) in anhydrous DMF (12 mL) under a Nitrogen atmosphere. After stirring for 45 minutes, intermediate **2** (0.44 g) was added. The mixture was stirred at r.t. for 14 hours, then it was diluted with AcOEt and washed with cold water. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 9:1 to 7:3) to give the title compound (0.955 g) as a colourless oil.
T.l.c.: CH/AcOEt 8:2, Rf=0.35.

MS (ES/+): m/z=571 $[M+Na]^+$.

Following the same procedure described for intermediate **14**, intermediates **15** and **16** were obtained.

Intermediate 15
1,1-Dimethylethyl 4-[1-({[1-(3,5-dichlorophenyl)ethyl]amino}carbonyl)-3-buten-1-yl]-4-(4-fluorophenyl)-1-piperidinecarboxylate (isomer 2)
Starting from intermediate **12** (0.77 g) and using intermediate **3**, 0.9 g of the title compound were obtained.
T.l.c.: CH/AcOEt 8:2, Rf=0.33.
MS (ES/+): m/z=571 $[M+Na]^+$.

Intermediate 16
1,1-Dimethylethyl 4-[1-({[1-(3-chloro-1-naphthalenyl)ethyl]amino}carbonyl)-3-buten-1-yl]-4-(4-fluorophenyl)-1-piperidinecarboxylate (isomer 2)
Starting from intermediate **12** (313 mg) and using intermediate **5**, 320 mg of the title compound were obtained.
T.l.c.: CH/AcOEt 7:3, Rf=0.45.
MS (ES/+): m/z=587 $[M+Na]^+$, 509 $[M-tBu+H]^+$.

Intermediate 17
1,1-Dimethylethyl 4-(4-fluorophenyl)-4-{1-[(methyloxy)carbonyl]-3-oxopropyl}-1-piperidinecarboxylate
Osmium tetraoxide 4% wt solution in water (135 µl) and $NaIO_4$ (190 mg) were added to a solution of intermediate **11** (180 mg) in THF (3.6 mL) and water (0.6 mL). A solution of $Na_2S_2O_5$ (100 mg) in a saturated sodium hydrogen carbonate solution (5 ml) was added and the resulting aqueous phase was extracted with AcOEt. The combined organic extracts were dried and concentrated *in vacuo* to give the title compound as a pale yellow oil (180 mg).
T.l.c.: CH/AcOEt 1:1, Rf=0.5.

Intermediate 18
1,1-Dimethylethyl 4-{1-[(3,5-dichlorophenyl)methyl]-2-oxo-3-pyrrolidinyl}-4-(4-fluorophenyl)-1-piperidinecarboxylate

3,5-Dichlorobenzylamine (117 mg) was added to a solution of intermediate **17** (180 mg) in dry dichloroethane (5 mL) under a Nitrogen atmosphere. After stirring for 1 hour at r.t. $NaBH(OAc)_3$ (169 mg) was added and the resulting mixture was stirred at r.t. overnight. Then it was diluted with DCM, washed with a saturated sodium hydrogen carbonate solution, dried and concentrated *in vacuo* to give a crude oil, which was purified by flash

chromatography (Biotage Flash 25M, CH/AcOEt 4:1). The two fractions corresponding to products with Rf=0.36 and Rf=0.50 (CH/AcOEt 1:1, detection with ninhydrine) were collected to give, after evaporation, an oil (40 mg) which was then dissolved, under a Nitrogen atmosphere, in dry MeOH (5 mL) and to which sodium methoxide (4.5 mg) was added. The mixture was refluxed for 5 hours, then it was allowed to cool to r.t. and solvent was removed *in vacuo*. The residue was dissolved in AcOEt, washed with a saturated sodium hydrogen carbonate solution, dried and concentrated *in vacuo*. The crude product thus obtained was purified by flash chromatography (CH/AcOEt 9:1) to give the title compound (35 mg) as a colourless oil.

T.l.c.: CH/ AcOEt 1:1, Rf=0.5.

NMR ($CDCl_3$): δ (ppm) 7.31 (dd, 2H); 7.2 (t, 1H); 6.98 (t, 2H); 6.83 (d, 2H); 4.25 (d, 1H); 4.04 (d, 1H); 3.76 (b, 2H); 3.01 (td, 1H); 2.88 (m, 1H); 2.82 (bm, 1H); 2.63 (dd, 1H); 2.41 (b, 1H); 2.18 (bd, 1H); 2.05-2.15 (m, 2H); 1.94 (b, 1H); 1.81 (b, 1H); 1.69 (m, 1H); 1.4 (s, 9H).

MS (ES/+): m/z=543 $[M+Na]^+$.

Intermediate 19

1,1-Dimethylethyl 4-{1-[(3,5-dichlorophenyl)methyl]-5-hydroxy-2-oxo-3-pyrrolidinyl}-4-(4-fluorophenyl)-1-piperidinecarboxylate

To a suspension of intermediate **13** (0.72 g) in THF (37.5 mL) and water (12.5 mL) osmium tetraoxide 4% wt solution in water (0.8 mL) was added. The mixture was stirred for 20 minutes during which it became dark, then $NaIO_4$ (1.15 g) was added portionwise in 10 minutes and the brownish reaction mixture was stirred at r.t. for 12 hours, thus becoming a milky suspension. The reaction mixture was diluted with AcOEt (250 mL) and washed with water (4 x 50 mL) and then with brine (40 mL). The organic phase was dried and concentrated *in vacuo* to give a brown-grey foam (0.635 g). This material was purified by flash chromatography (Biotage Flash 40S, CH/AcOEt 6:4 to 1:1) affording the title compound (0.335 g) as a white foam.

T.l.c.: CH/AcOEt 1:1, Rf=0.33 (detection with ninhydrine)

NMR ($CDCl_3$): δ (ppm) 7.32 (dd, 2H); 7.21 (s, 1H); 6.98 (t, 2H); 6.78 (s, 2H); 4.61 (d, 1H); 4.45 (bt, 1H); 3.91 (d, 1H); 3.85 – 3.68 (bm, 2H); 3.05 (t, 1H); 2.95 – 2.78 (bm, 2H); 2.25 – 2.15 (m, 3H); 2.11 – 1.60 (m, 3H); 1.39 (s, 9H).

MS (ES/+): m/z=559 $[M+Na]^+$.

Intermediate 20

1,1-dimethylethyl 4-[1-({[(3,5-dichlorophenyl)methyl]amino}carbonyl)-3-oxopropyl]-4-(4-fluorophenyl)-1-piperidinecarboxylate (isomer 1)

To a suspension of intermediate **14** (0.07 g) in THF (2 mL) and water (0.5 mL) osmium tetraoxide 4% wt solution in water (3.2 mL) was added. The mixture was stirred r.t. for 1 hour during which it became dark, then $NaIO_4$ (0.082 g) was added portionwise and the brownish reaction mixture was stirred at r.t. for 1 hour. After this time it was diluted with

water and extracted with AcOEt. The organic layer was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 9:1 to 7:3) to afford the title compound as a yellow oil (0.047 g). T.l.c.: CH/AcOEt 6:4, Rf=0.37 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 9.70 (s, 1H); 7.24 (s, 2H); 7.13 (dd, 2H); 6.96 (s, 1H); 6.93 (t, 2H); 5.40 (bq, 1H); 3.96 - 3.82 (m, 2H); 3.02 (dd, 1H); 2.71 – 2.35 (m, 4H); 2.11 - 1.85 (m, 2H); 1.74 – 1.57 (m, 2H); 1.39 (s, 9H); 1.33 (d, 3H).
MS (ES/+): m/z=573 $[M+Na]^+$.

Example 1
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one
To intermediate **19** (0.22 g), TFA (15 mL) was added and the solution was heated at 60°C under a Nitrogen atmosphere for 3 hour. The reaction mixture was evaporated *in vacuo*, the residue dissolved in DCM (30 mL) and slowly added to a 2.5M sodium hydroxide solution, previously cooled to 0°C. The organic phase was separated and the basic aqueous solution was extracted with DCM (40 mL); the collected organic phases were dried and concentrated *in vacuo* to give the crude title compound (0.17 g) as a yellow oil, which was purified by flash chromatography (DCM, then DCM/MeOH from 95:5 to 7:3) to give the title compound (104 mg) as a white solid.
T.l.c.: DCM/MeOH 9:1, Rf=0.15 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 7.34 (dd, 2H); 7.23 (t, 1H); 6.99 (t, 2H); 6.97 (m, 2H); 6.68 (t, 1H); 4.46 (s, 2H); 3.75 (dd, 2H); 2.89 (t, 4H); 2.53 (m, 2H); 2.23 (m, 2H).
MS (ES/+): m/z=419 $[M+H]^+$.

Example 2
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one hydrochloride
To a suspension of example **1** (15 mg) in dry Et2O (0.5 mL) at 0°C, hydrogen chloride (1M solution in Et2O - 39 µL) was added dropwise, the resulting thick suspension was stirred at 0°C for 15 minutes, then solvent was evaporated under a Nitrogen flux and the solid residue was triturated in pentane (3 x 1 mL) to obtain the title compound (16 mg) as a white solid.
NMR (d_6-DMSO): δ (ppm) 8.52 (bs, 2H); 7.52 (t, 1H); 7.42 (dd, 2H); 7.2 - 7.16 (m, 5H); 4.51 (s, 2H); 3.97 (s, 2H); 3.12 – 3.0 (m, 4H); 2.78 (d, 2H); 2.3 (m, 2H).
MS (ES/+): m/z=419 $[M-HCl+H]^+$.

Example 3
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one
To a solution of example **1** (16.1 g) in CH3CN (200 mL) 37%wt formaldehyde in water (6.5 mL) was added, the resulting mixture was stirred at r.t. for 15 minutes then $NaBH(OAc)_3$ (12.2 g) was added portionwise (exothermic reaction observed). The

reaction mixture was stirred at r.t. for 1 hour, then it was quenched with aqueous 5% sodium hydrogen carbonate solution (40 ml), CH3CN was evaporated and the residue was diluted with further aqueous 5% sodium hydrogen carbonate solution (200 mL) and extracted with DCM (3 x 200 mL). The collected organic phases were dried, concentrated *in vacuo* to give a crude white foam (16.5 g) which was purified by flash chromatography (Biotage Flash 75L, DCM , then DCM/MeOH from 95:5 to 8:2). The title compound (12.7 g) was obtained as a white solid.
T.l.c.: DCM/MeOH 9:1, Rf = 0.41 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 7.35 (dd, 2H); 7.23 (t, 1H); 6.98 (t, 2H); 6.96 (m, 2H); 6.76 (bt, 1H); 4.46 (s, 2H); 3.76 (dd, 2H); 2.70 - 2.25 (bm, 8H); 2.23 (s, 3H).
MS (ES/+): m/z=433 $[M+H]^+$.

Example 4

1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one hydrochloride

To a suspension of example **3** (10.7 g) in dry Et2O (200 mL) at 0°C, hydrogen chloride (1M solution in Et2O - 26 mL) was added dropwise, the resulting thick suspension was stirred at 0°C for 1 hour, then it was filtered under a Nitrogen atmosphere on a Gooch filter and washed with Et2O (2 x 100 mL) and with pentane (3 x 100 mL), then dried *in vacuo* at 40°C for 3 hours and at r.t. for 14 hours. The title compound (11.2 g) was obtained as a white solid.
NMR (d_6-DMSO): δ (ppm) 9.97 (b, 1H); 7.51 (bs, 1H); 7.40 (s, 1H); 7.36 (dd, 2H); 7.16 (d, 2H); 7.15 (t, 2H); 4.51 (s, 2H); 4.01 (s, 2H); 3.55 - 3.3 (m, 2H); 3.04 (bd, 1H); 2.96 (bdd, 1H); 2.76 (d, 3H); 2.55 - 2.3 (m, 2H); 2.13 (bt, 2H).
MS (ES/+): m/z=433 $[M-HCl+H]^+$.

Example 5

1-[1-(3,5-Dichlorophenyl)ethyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one (enantiomer 1)

TFA (0.8 mL) was added to intermediate **20** (0.019 g) and the mixture was allowed to stir at 60°C for 1 hour. After this time the mixture was cooled to r.t. and concentrated *in vacuo*. The crude thus obtained was diluted with DCM and poured into a 2M sodium hydroxide solution previously cooled to 0°C. The organic layer was separated then was dried and concentrated *in vacuo* to give a residue which was purified by flash chromatography (DCM, then DCM/MeOH from 95:5 to 8:2) to give the title compound (0.014 g) as a white foam.
T.l.c.: DCM/MeOH 9:1, Rf=0.39 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 7.37 (dd, 2H); 7.27 (m, 1H); 7.06 (d, 2H); 7.04 (t, 2H); 6.72 (s, 1H); 5.40 (q, 1H); 3.88 (dd, 1H); 3.60 (dd, 1H); 2.96 (m, 4H); 2.62 (m, 2H); 2.27 (m, 2H); 1.56 (d, 3H).
MS (ES/+): m/z=433 $[M+H]^+$.

Example 6

1-[1-(3,5-Dichlorophenyl)ethyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one (enantiomer 2)

To a suspension of intermediate **15** (0.9 g) in THF (20 mL) and water (5 mL) osmium tetraoxide 4% wt solution in water (1.5 mL) was added. The mixture was stirred at r.t. for 1 hour during which it became dark, then $NaIO_4$ (1.4 g) was added and the brownish reaction mixture was stirred at r.t. for 14 hours. After this time it was diluted with water and extracted with AcOEt. The organic layer was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 9:1 to 7:3) and the fractions with Rf=0.37 (CH/AcOEt 6:4, detection with ninhydrine) and MS (ES/+): m/z=573 $[M+Na]^+$ were collected to give an intermediate (0.4 g) to which TFA (0.8 mL) was added and the mixture was allowed to stir at 60°C for 2 hours. After this time the mixture was cooled to r.t. and concentrated *in vacuo*. The crude thus obtained was diluted with DCM and poured into a 2M sodium hydroxide solution previously cooled to 0°C. The organic layer was separated then was dried and concentrated *in vacuo* to give a residue which was purified by flash chromatography (DCM, then DCM/MeOH from 95:5 to 8:2) to give the title compound (0.065 g) as a white foam.

T.l.c.: DCM/MeOH 9:1, Rf=0.39 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.37 (dd, 2H); 7.27 (m, 1H); 7.06 (d, 2H); 7.04 (t, 2H); 6.72 (s, 1H); 5.40 (q, 1H); 3.88 (dd, 1H); 3.60 (dd, 1H); 2.96 (m, 4H); 2.62 (m, 2H); 2.27 (m, 2H); 1.56 (d, 3H).

MS (ES/+): m/z=433 $[M+H]^+$.

Example 7

1-[1-(3-Chloro-1-naphthalenyl)ethyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one (enantiomer 2)

To a suspension of intermediate **16** (0.32 g) in THF (16 mL) and water (4 mL) osmium tetraoxide 4% wt solution in water (1 mL) was added. The mixture was stirred at r.t. for 45 minutes, then $NaIO_4$ (0.5 g) was added portion wise and the reaction mixture was stirred at r.t. for 1 hour. After this time it was diluted with water and extracted with AcOEt. The organic layer was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 9:1 to 7:3) and the fractions with Rf=0.78 and Rf=0.63 (CH/AcOEt 1:1, detection with ninhydrine) and both having MS (ES/+): m/z=589 $[M+Na]^+$ were collected to give a mixture of intermediates (0.068 g) to which TFA (2 mL) was added and the mixture was allowed to stir at 60°C for 2 hours. After this time the mixture was cooled to r.t. and concentrated *in vacuo*. The crude thus obtained was diluted with DCM and poured into a 2M sodium hydroxide solution previously cooled to 0°C. The organic layer was separated then was dried and concentrated *in vacuo* to give the title compound (0.05 g) as a white foam.

T.l.c.: DCM/MeOH 8:2, Rf=0.77 (detection with ninhydrine).

Example 8

1-[1-(3,5-Dichlorophenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one (enantiomer 1)

To a solution of example **5** (0.241g) in CH3CN (14 mL) 37%wt formaldehyde in water (0.130 mL) was added. The resulting mixture was stirred at r.t. for 15 minutes then $NaBH(OAc)_3$ (0.235 g) was added. The reaction mixture was stirred at r.t. for 1 hour, then it was quenched with water, CH3CN was evaporated and the residue was diluted with water and extracted with DCM. The collected organic phases were dried, concentrated in vacuo to give a crude that was purified by flash chromatography (DCM, then DCM/MeOH from 98:2 to 9:1) to give the title compound (0.177 g) as a white solid.
T.l.c.: DCM/MeOH 85:15, Rf=0.54 (detection with ninhydrine).
MS (ES/+): m/z=447 $[M+H]^+$.

Following the same procedure described for example **8**, example **9** and **10** were obtained.

Example 9

1-[1-(3,5-Dichlorophenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one (enantiomer 2)

Starting from example **6** (0.10 g), 0.025 g of the title compound were obtained.
T.l.c.: DCM/MeOH 85:15, Rf=0.5 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 7.39 (dd, 2H); 7.28 (m, 1H); 7.08 - 7.06 (m, 4H); 6.82 (bs, 1H); 5.36 (q, 1H); 3.89 - 3.62 (dd, 2H); 3.3 - 2.2 (bm, 8H); 2.65 (s, 3H); 1.53 (d,3H).
MS (ES/+): m/z=447 $[M+H]^+$.

Example 10

1-[1-(3-Chloro-1-naphthalenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one (enantiomer 2)

Starting from example **7** (0.050 g), 0.024 g of the title compound were obtained.
T.l.c.: DCM/MeOH 85:15, Rf=0.6 (detection with ninhydrine).
MS (ES/+): m/z=463 $[M+H]^+$.

Example 11

1-[1-(3,5-Dichlorophenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one hydrochloride(enantiomer 1)

Hydrogen chloride (1M solution in Et2O – 0.43 mL) was added to a solution of example **8** (0.176 g) in dry Et2O (4 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 15 minutes, then it was concentrated *in vacuo*. The residue was triturated with pentane (3 x 1 mL) to give the title compound (0.180 g) as a white solid.
NMR (d_6-DMSO): δ (ppm) 10.11/9.94 (2bs, 1H); 7.51 - 7.46 (m, 1H); 7.41 (bs, 1H); 7.32 (dd, 2H); 7.2 – 7.1 (m, 4H); 5.11 (m, 1H); 4.14 - 3.74 (dd, 2H); 3.3 - 2.13 (bm, 8H); 2.77 (d, 3H); 1.52 (d, 3H).
MS (ES/+): m/z=447 $[M-HCl+H]^+$.

Example 12

1-[1-(3-Chloro-1-naphthalenyl)ethyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one hydrochloride (enantiomer 2)

Hydrogen chloride (1M solution in Et2O – 57 µL) was added to a solution of example **10** (0.024 g) in dry Et2O (1 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 15 minutes, then it was concentrated *in vacuo*. The residue was triturated with pentane (3 x 1 mL) to give the title compound (0.024 g) as a white solid.

NMR (d_6-DMSO): δ (ppm) 9.57 (bs, 1H); 8.01 (s, 1H); 7.92 (d, 1H); 7.88 (bd, 1H); 7.55 (t, 1H); 7.47 (s, 1H); 7.40 (t, 1H); 7.3 - 6.5 (bm, 5H); 5.87 (q, 1H); 4.1 - 3.9 (bm, 1H); 3.2 - 2.0 (bm, 12H); 1.61 (bs, 3H).

MS (ES/+): m/z=463 $[M-HCl+H]^+$.

Example 13

1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-2-pyrrolidinone

TFA (200 µl) was added to a solution of intermediate **18** (35 mg) in dry DCM (1.8 mL) and the mixture was stirred for 3 hours at r.t. Then it was diluted with DCM, washed with a saturated sodium hydrogen carbonate solution, dried and concentrated *in vacuo*. The residue was purified by SCX to give the title compound (22 mg) as a colourless oil.

T.l.c.: DCM/MeOH 2:8, Rf=0.16.

NMR (d_6-DMSO): δ (ppm) 7.43 (t, 1H); 7.36 (dd, 2H); 7.06 (t, 2H); 6.96 (d, 2H); 5.34 (bs, 1H); 4.27 (d, 1H); 4.04 (d, 1H); 2.94 (dd, 2H); 2.89 (m, 1H); 2.72 (t, 1H); 2.6 (m, 1H); 2.58 (m, 1H); 2.49 (m, 1H); 2.41 (dd, 1H); 2.16 (bd, 1H);1.95 (m, 2H); 1.82 (m, 1H); 1.56 (m, 1H).

MS (ES/+): m/z=421 $[M+H]^+$.

Example 14

1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-2-pyrrolidinone

37% wt Formaldehyde in water (8 µL) and $NaBH(OAc)_3$ (16 mg) were added to a solution of example **13** in CH3CN (3 mL). After stirring for 2 hour the same amounts of 37% wt formaldehyde in water and $NaBH(OAc)_3$ were added and the mixture was stirred at r.t. overnight. Then it was diluted with DCM (2 ml), washed with a saturated sodium hydrogen carbonate solution and filtered on a phase separation cartridge. The filtered was concentrated *in vacuo* and the crude product was purified by flash chromatography (DCM/MeOH 4:6) to give the title compound (15 mg) as a colourless oil.

T.l.c.: DCM/MeOH 4:6, Rf=0.15 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 7.43 (t, 1H); 7.34 (dd, 2H); 7.03 (t, 2H); 6.95 (s, 2H); 4.28 (d, 1H); 4.02 (d, 1H); 2.9 (dd, 1H); 2.69 (m, 1H); 2.4 - 2.52 (m, 2H); 2.41 (dd, 1H); 2.0 - 2.2 (m, 2H); 2.0 (s, 3H); 1.8 - 2.05 (m, 5H); 1.61 (m, 1H).

MS (ES/+): m/z=435 $[M+H]^+$.

Example 15

1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-onefumarate salt

Example **3** (250mg) was dissolved in MeOH (2.5 mL) at r.t. under Nitrogen atmosphere. The clear solution was seeded and fumaric acid (67 mg) was added. Solid crystallization was observed. The slurry was stirred 16 hours at r.t. The solid was filtered and dried at r.t. under vacuum to give the title compound (227 mg).

NMR :(d_6-DMSO) δ(ppm) 7.51 (t, 1H); 7.41 (dd, 2H); 7.13 (t, 2H); 7.13 (m, 2H); 7.13 (m, 1H); 6.55 (s, 2H); 4.50 (s, 2H); 3.96 (s, 2H); 2.78 (bm, 2H); 2.70 (bm, 2H); 2.62 (bm, 2H); 2.24 (bm, 2H); 2.38 (s, 3H).

m.p. (by DSC): 205.8°C

Table 1

The X-ray powder diffraction pattern of the product of Example 15 in terms of 'd' spacings is as follows

Two theta (deg)	d-spacing (Angstroms)
4,2	21,1
9,2	9,6
11,4	7,8
12,1	7,3
12,5	7,1
14,0	6,3
16,1	5,5
16,3	5,4
16,7	5,3
17,0	5,2
17,3	5,1
17,9	5,0
18,2	4,9
18,6	4,8
19,0	4,7
20,1	4,4
21,0	4,2
21,2	4,2
23,2	3,8
23,6	3,8
23,8	3,7
24,4	3,6
25,2	3,5
26,7	3,3
27,8	3,2
28,5	3,1
28,7	3,1
29,5	3,0
30,4	2,9
33,8	2,7
34,7	2,6
35,9	2,5
38,1	2,4

Example 16

1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-onecitrate salt

Example **3** (200mg) was dissolved in tetrahydrofuran (2 mL) at r.t. under Nitrogen atmosphere. The clear solution was seeded and a solution of citric acid (88 mg) in MeOH (0.5 mL) was dosed. Solid crystallization was observed. The slurry was stirred 16 hours at r.t.. The solid was filtered and dried at r.t. under vacuum to give the title compound (200 mg).NMR (d_6-DMSO) δ(ppm) 11.6-10.4 (b, 3H); 7.52 (t, 1H); 7.42 (dd, 2H); 7.17 (t, 2H); 7.16 (m, 2H); 7.16 (m, 1H); 4.51 (s, 2H); 3.96 (s, 2H); 3.06-2.97 (bm, 4H); 2.82 (bm, 2H); 2.29 (bm, 2H); 2.65 (s, 3H); 2.60 (d, 2H); 2.52 (d, 2H)

m.p. (by DSC): 156.6 °C

Table 2

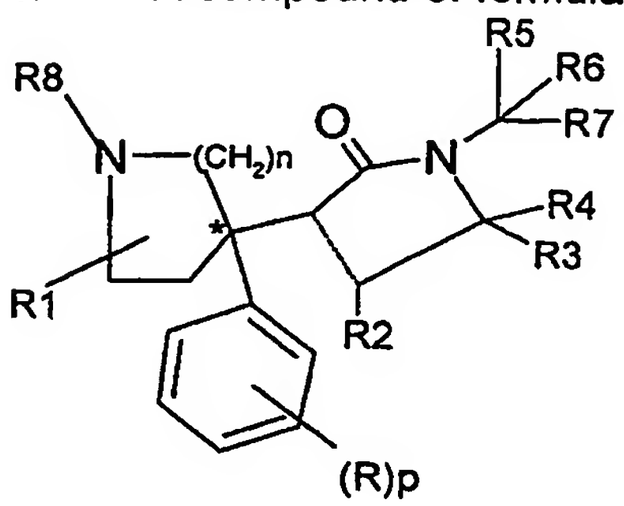
The X-ray powder diffraction pattern of the product of Example 16 in terms of 'd' spacings is as follows

Two theta (deg)	d-spacing (Angstroms)
7,1	12,5
10,6	8,4
11,6	7,7
11,9	7,4
14,0	6,3
14,5	6,1
16,0	5,5
16,8	5,3
17,6	5,0
18,5	4,8
19,5	4,6
19,9	4,5
20,6	4,3
21,2	4,2
21,8	4,1
22,4	4,0
23,1	3,9
23,6	3,8
24,0	3,7
24,9	3,6
25,5	3,5
26,4	3,4
28,1	3,2
29,1	3,1
29,7	3,0
32,9	2,7

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A compound of formula (I)



(I)

—— represents single or double bond;

R represents halogen, C_{1-4} alkyl, cyano, C_{1-4} alkoxy, trifluoromethyl or trifluoromethoxy;

R_1 represents hydrogen, halogen, C_{3-7} cycloalkyl, hydroxy, nitro, cyano or C_{1-4} alkyl optionally substituted by one or two groups selected from halogen, cyano, hydroxy or C_{1-4} alkoxy;

R_2 represents hydrogen or C_{1-4} alkyl;

R_3 represents hydrogen, hydroxy or C_{1-4} alkyl;

R_4 represents hydrogen or R_4 together with R_3 represents =O;

R_5 represents phenyl, naphthyl, a 9 to 10 membered fused bicyclic heterocyclic group or a 5 or 6 membered heteroaryl group, wherein said groups are optionally substituted by 1 to 3 groups independently selected from trifluoromethyl, C_{1-4} alkyl, hydroxy, cyano, C_{1-4} alkoxy, trifluoromethoxy, halogen or $S(O)qC_{1-4}$ alkyl;

R_6 and R_7 independently represent hydrogen, cyano, C_{1-4} alkyl or R_3 together with R_4 represents C_{3-7} cycloalkyl;

R_8 represents $(CH_2)rR_9$;

R_9 represents hydrogen or C_{3-7} cycloalkyl;

n represents 1 or 2;

p is zero or an integer from 1 to 3;

q is 0, 1 or 2;

r is 0 or an integer from 1 to 4;

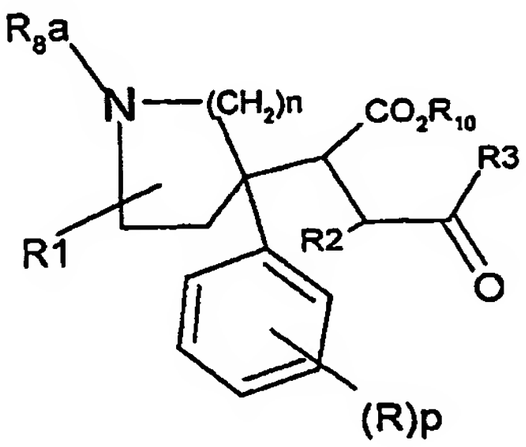
and pharmaceutically acceptable salts and solvates thereof.

2. A compound selected from:

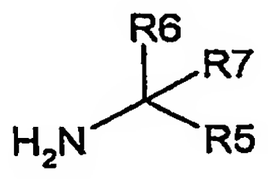
1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one;

1-[(3,5-Dichlorophenyl)methyl]-3-[4-(4-fluorophenyl)-1-methyl-4-piperidinyl]-1,5-dihydro-2*H*-pyrrol-2-one;
amorphous and crystalline forms thereof and phamaceutically acceptable salts (e.g hydrochloride, fumarate or citrate) and solvates thereof.

3. A process (A) for the preparation of a compound as claimed in claim 1), wherein -- -- is a single bond, R_3 represents hydrogen or C_{1-4} alkyl and R_4 represents hydrogen, which comprises reductive N-alkylation of a compound of formula (II)



(II)

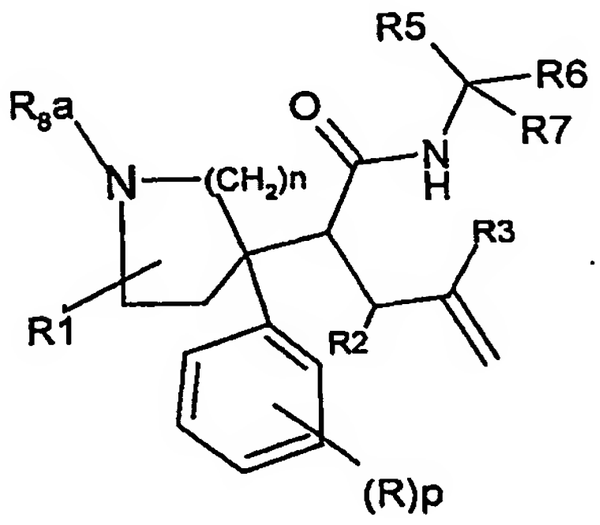


(III)

in which R_{10} is methyl or ethyl, R_3 is hydrogen or C_{1-4} alkyl and R_{8a} has the meaning defined in formula (I) or is a nitrogen protecting group, with the amine (III), followed by cyclisation reaction in the presence of an alkali metal base;

or

a process (B) for the preparation of a compound as claimed in claim 1, wherein --- is a single bond, R_3 is hydroxy and R_4 is hydrogen, comprising the oxidation of an allyl derivative of formula (V),

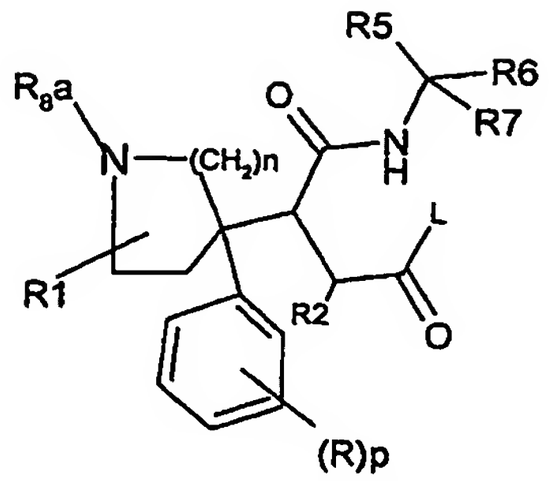


(V)

in which R_{8a} is defined as in formula (I) or is a nitrogen protecting group and R_3 is hydrogen, followed by in situ cyclisation;

or

a process (C) for the preparation of a compound as claimed in claim 1, wherein ---- is a single bond and R_3 together with R_4 represents =O, comprising cyclisation of a compound of formula (VII),

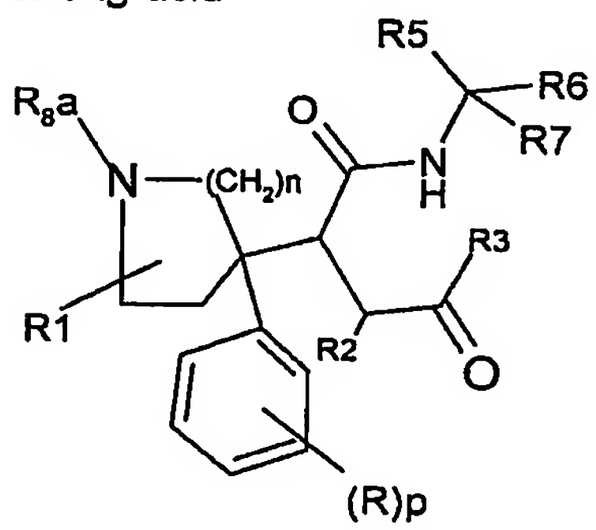


(VII)

wherein R_{8a} is defined as in formula (II) and L is a suitable leaving group, in the presence of an organic base;

or

a process (D) for the preparation of a compound as claimed in claim 1, wherein ----is a double bond, R_3 represents hydrogen or C_{1-4} alkyl and R_4 is hydrogen, comprising cyclisation of a compound of formula (VI), in which R_3 represents hydrogen or C_{1-4} alkyl and R_{8a} is defined as in formula (I) or is a nitrogen protecting group, in the presence of a strong acid



(VI)

in which R_3 represents hydrogen or C_{1-4} alkyl, in the presence of a strong acid;

or

a process (E) for the preparation of a compound as claimed in claim 1, wherein ---- is a double bond and R_3 is hydroxy or R_3 together with R_4 represents =O comprising reaction of a compound of formula (I) wherein —— is a single bond, R_8 has the meaning defined in formula (I) or is a nitrogen protecting group and R_3 is hydroxy protected group or R_3 together with R_4 represents =O, with a brominating agent followed by treatment with a base;

or

a process (F) for the preparation of a compound as claimed in claim 1, wherein R_8 is $(CH_2)rR_9$ wherein r is an integer from 1 to 4 , comprising reductive alkylation of a compound of formula(I), wherein R_8 is hydrogen, with $CH(O)(CH_2)_mR_9$ (VIII), wherein m is an integer from 0 to 3;

and processes A,B,C,D E and F are followed where necessary or desired by one or more of the following steps:
i) removal of any protecting group;
ii) isolation of the compound as a salt thereof;
iii) separation of a compound of formula(I) or a derivative thereof into the enantiomers thereof.

4. A compound as claimed in claims 1 or 2 for use in therapy.

5. The use of a compound as claimed in claims 1 or 2 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

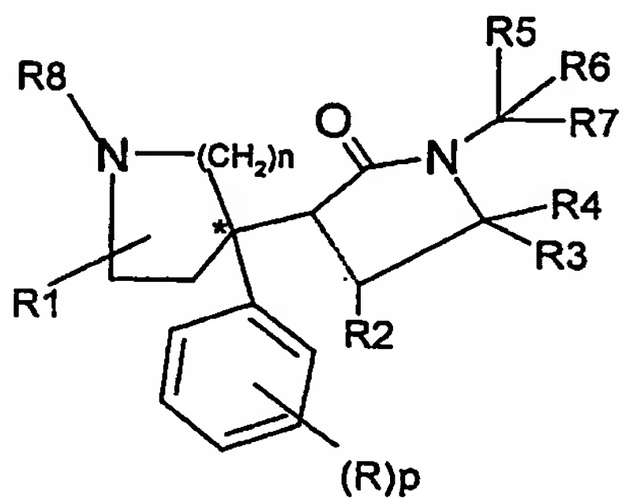
6. The use of a compound as claimed in claims 1 or 2 in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

7. A pharmaceutical composition comprising a compound as claimed in claims 1 or 2 in admixture with one or more pharmaceutically acceptable carriers or excipients.

8. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein comprising administration of an effective amount of a compound of formula (I) as claimed in claims 1 or 2.

ABSTRACT

The present invention relates to novel compounds of formula (I)



(I)

---- represents single or double bond;

R represents halogen, C_{1-4} alkyl, cyano, C_{1-4} alkoxy, trifluoromethyl or trifluoromethoxy;

R_1 represents hydrogen, halogen, C_{3-7} cycloalkyl, hydroxy, nitro, cyano or C_{1-4} alkyl optionally substituted by one or two groups selected from halogen, cyano, hydroxy or C_{1-4} alkoxy;

R_2 represents hydrogen or C_{1-4} alkyl;

R_3 represents hydrogen, hydroxy or C_{1-4} alkyl;

R_4 represents hydrogen or R_4 together with R_3 represents =O;

R_5 represents phenyl, naphthyl, a 9 to 10 membered fused bicyclic heterocyclic group or a 5 or 6 membered heteroaryl group, wherein said groups are optionally substituted by 1 to 3 groups independently selected from trifluoromethyl, C_{1-4} alkyl, hydroxy, cyano, C_{1-4} alkoxy, trifluoromethoxy, halogen or $S(O)qC_{1-4}$ alkyl;

R_6 and R_7 independently represent hydrogen, cyano, C_{1-4} alkyl or R_3 together with R_4 represents C_{3-7} cycloalkyl;

R_8 represents $(CH_2)rR_9$;

R_9 represents hydrogen or C_{3-7} cycloalkyl;

n represents 1 or 2;

p is zero or an integer from 1 to 3;

q is 0, 1 or 2;

r is 0 or an integer from 1 to 4;

and pharmaceutically acceptable salts and solvates thereof; process for their preparation and their use in the treatment of conditions mediated by tackykinins and/or by selective inhibition of serotonin reuptake transporter protein .